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Abstract: In order to determine knowledge, attitudes and practices towards malaria prophylaxis, as well as its side-effects and efficacy, a self-administered questionnaire was distributed to European travellers on return flights from tropical Africa to Europe. Between 1985 and 1988 the questionnaire was completed by 44,472 passengers (80.1% of those on board) on 242 flights. A follow-up questionnaire was completed by 42,202 (94.9%) of the same travellers 3 months later. Almost all knew about the risk of malaria, but 10% relied solely on advice from nonmedical sources. While 55.6% had taken at least one measure against mosquito bites, only 4.5% adopted three such measures (used repellents and insecticides and wore long clothing after dusk). Compliance with chemoprophylaxis use was reported by 57.0% of travellers who spent less than 3 months in Africa, compared with 29.2% who stayed 3-12 months. Depending on the antimalaria regimen taken, 11-44% of the travellers experienced adverse effects, while four deaths were attributed to the chemoprophylaxis. The incidence of malaria per month of exposure for travellers who took no chemoprophylaxis was 15.2 per 1000 in East Africa and 24.2 per 1000 in West Africa. In East Africa, the prophylactic efficacy of the currently recommended antimalaria regimens (relative to that of no chemoprophylaxis) was zero for a chloroquine dosage of 300 mg base per week (4 malaria fatalities), 64.1% for a chloroquine dosage of 600 mg base per week ($P = 0.03$), and 94.0% for mefloquine ($P = 0.003$).

Research/Recherche

Malaria chemoprophylaxis among European tourists in tropical Africa: use, adverse reactions, and efficacy

R. Steffen,[1] R. Heusser,[2] R. Mächler,[2] R. Bruppacher,[3] U. Naef,[4] D. Chen,[4] A.M. Hofmann,[2] & B. Somaini[5]

In order to determine knowledge, attitudes and practices towards malaria prophylaxis, as well as its side-effects and efficacy, a self-administered questionnaire was distributed to European travellers on return flights from tropical Africa to Europe. Between 1985 and 1988 the questionnaire was completed by 44 472 passengers (80.1% of those on board) on 242 flights. A follow-up questionnaire was completed by 42 202 (94.9%) of the same travellers 3 months later. Almost all knew about the risk of malaria, but 10% relied solely on advice from nonmedical sources. While 55.6% had taken at least one measure against mosquito bites, only 4.5% adopted three such measures (used repellents and insecticides and wore long clothing after dusk). Compliance with chemoprophylaxis use was reported by 57.0% of travellers who spent less than 3 months in Africa, compared with 29.2% who stayed 3–12 months. Depending on the antimalaria regimen taken, 11–44% of the travellers experienced adverse effects, while four deaths were attributed to the chemoprophylaxis. The incidence of malaria per month of exposure for travellers who took no chemoprophylaxis was 15.2 per 1000 in East Africa and 24.2 per 1000 in West Africa. In East Africa, the prophylactic efficacy of the currently recommended antimalaria regimens (relative to that of no chemoprophylaxis) was zero for a chloroquine dosage of 300 mg base per week (4 malaria fatalities), 64.1% for a chloroquine dosage of 600 mg base per week ($P = 0.03$), and 94.0% for mefloquine ($P = 0.003$).

Introduction

As chloroquine-resistant *Plasmodium falciparum* continues to spread in Africa, data are needed to formulate malaria chemoprophylaxis recommendations for non-immune travellers who visit such areas. However, data which would allow a balance to be made between the risk of infection and the protection afforded by prevention measures and their possible risk are far from complete (*1*).

The incidence of malaria among such travellers is not known, and estimates of the risk of infection have so far been based mainly on malaria surveillance, even though the infections may have been treated abroad and notification of illness upon return has been incomplete. The case-fatality rate of imported *P. falciparum* malaria varies between 0.6% and 7% (*1*, *2*). Recent studies have assessed the efficacy of personal protection measures against mosquito bites (*3*, *4*), but compliance by non-immune individuals has not been investigated. Two surveys have compared the efficacy of various chemoprophylaxis regimens among nonimmune residents abroad. The results of one of these studies are difficult to interpret (*5*), while the other compared only chloroquine + proguanil versus chloroquine + pyrimethamine/sulfadoxine (PYR/SDX, Fansidar®) (*6*), the last drug combination being no longer recommended. Drug trials in semi-

[1] Head, Division of Epidemiology and Prevention of Communicable Diseases, Institute of Social and Preventive Medicine, University of Zurich, Sumatrastrasse 30, CH-8006 Zurich, Switzerland. Requests for reprints should be sent to this address.

[2] Resident, Division of Epidemiology and Prevention of Communicable Diseases, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland.

[3] Associate Professor, Division of Social and Preventive Medicine, University of Basle, Basle, Switzerland.

[4] F. Hoffmann–La Roche Ltd, Basle, Switzerland.

[5] Vice-Director, Federal Office of Public Health, Bern, Switzerland.

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immune volunteers, *in vitro* tests, and therapeutic studies are not reliable predictors of prophylactic efficacy in non-immune travellers (*4, 7*). The incidence of adverse drug reactions associated with 4-aminoquinoline chemoprophylaxis has been determined mainly in studies with the higher doses used to treat malaria or other conditions, e.g., rheumatic diseases (*8*). Also, uncertainty exists about rare adverse reactions to new drugs, since they cannot be detected during premarketing drug trials (*9*).

The occurrence of severe, sometimes fatal, adverse reactions associated with PYR/SDX and with amodiaquine have been investigated previously (*10–14*).[a] Initial studies on malaria prophylaxis among travellers were unable to conduct follow-up investigations (*15*);[b] it is, however, essential to include the period after returning home in such studies, since malaria and any adverse effects might occur also in this period. Because in many European countries the law allows such follow-up, we carried out such a study to assess the use, safety and efficacy of the malaria prophylaxis used by short-term European visitors to Africa.

Study population and methods

Between April 1985 and July 1988, a self-administered questionnaire was distributed and collected by cabin crews to all passengers flying back to Europe from East Africa (Kenya) or West Africa (9 countries) on board two charter airlines (Balair, Switzerland, and LTU, Federal Republic of Germany). Similarly, Swissair passengers on nine flights were questioned. The questionnaire, in four languages, covered traveller's demographics and home address, pretravel sources of health information, use of protective measures against mosquito bites, use of chemoprophylaxis, any adverse reactions associated with the chemoprophylaxis in the opinion of the traveller, and illness abroad. A second questionnaire was mailed to the travellers 3 months later. This inquired about drug use, adverse reactions and illness upon return. Nonrespondents to the second questionnaire were sent an additional copy or interviewed on the telephone. All physicians who treated patients in Africa or Europe for severe adverse drug reactions that required hospitalization, or for malaria that was confirmed by a blood film, were contacted by mail or given a personal interview to provide a case report.

To ensure the completeness of detection of malaria infections and severe adverse drug reactions, air rescue organizations and the embassies of European countries in Africa were asked to report any request for air evacuation and any fatality that was potentially caused by chemoprophylaxis or malaria.

The results from all the travellers who responded were included in the analysis, except those from individuals who had remained in Africa for more than 1 year. "Compliant" travellers were those who had started chemoprophylaxis at least 2 days prior to arriving in Africa, had not missed a dose, and had continued taking the medication for at least 4 weeks after return or until the onset of malaria symptoms. Severe adverse drug reactions were defined as those that required hospitalization in situations where any possible association with chemoprophylaxis was suspected by the attending physician. To calculate the incidence of such reactions, only definite or probable associations were accepted (*16*). Cases of malaria were included if they had been confirmed by the results of a blood smear provided by the attending physician or if the patients were able to give a clear report on the results of their smear, including, e.g., the parasite species involved. Drug efficacy was analysed only for compliant travellers. The prophylactic efficacy of the various chemoprophylaxis regimens was calculated by dividing the difference between the incidence of malaria among those who had not used specific chemoprophylaxis and those who had, by the incidence among those who had not used chemoprophylaxis.

Various drug regimens were recommended by different national bodies during the study period; prophylaxis with 4-aminoquinoline at various dosages was recommended to all travellers who visited West Africa. In contrast, travellers from Austria (until the end of 1986), the Federal Republic of Germany, or Switzerland (until mid-1985) who visited East Africa were advised to use chloroquine (or amodiaquine) plus PYR/SDX weekly. Subsequently, travellers from the Federal Republic of Germany were recommended to take chloroquine weekly with PXR/SDX, whereas those from Switzerland were recommended to take PYR/SDX weekly with mefloquine. Until mid-1986, travellers from France were advised to take 4-aminoquinoline daily, and thereafter mefloquine weekly. Finally, Italian travellers were most recommended to use 500 mg sulfalene and 25 mg pyrimethamine (Metakelfin®) weekly.

All questionnaires were reviewed by one of us. The results from the first and second questionnaires were pooled; if an adverse drug reaction was reported in both the first and the second questionnaire, it was counted only once. In instances where the replies

[a] **Freyenmuth, T.** [*Agranulocytosis and liver damage caused by amodiaquine*]. Thesis, University of Zurich, 1987 (in German).

[b] **Phillips-Howard, P.A.** *The epidemiology of malaria in Britain.* Thesis, University of London, 1988.

were inconsistent, the travellers were contacted. Data were analysed using the SAS™ software package. The incidences of adverse reactions were compared using χ^2 tests and the statistical significance was defined as $P<0.01$. Multiple logistic regression was used to analyse dichotomous dependent variables by means of the SAS–CATMOD procedure. The influence of additional variables was described by comparing the probabilities of the observed P(obs) and expected P(exp) outcomes, as calculated by multiple logistic regression (*17*).

Results

Of the 55 767 passengers on board the 233 charter and 9 scheduled flights, 44 667 (80.1%) completed the first questionnaire. From these, 195 long-term visitors were excluded. Of the remaining 44 472 travellers, 42 202 (94.9%) replied to the second questionnaire (Table 1). For 54.9%, the journey was their first ever visit to the tropics. A total of 93.4% of the travellers stated that they were on vacation in Africa, 2.2% to visit friends or relatives, 1.6% to work (usually a long trip) or study, and 1.5% for business (short trip); 92.3% stayed in Africa for 3 weeks or less. The country of residence of the travellers is shown in Table 2.

Table 1: **Demographic characteristics of the study population of travellers to East or West Africa**

	Travel destination: East Africa	West Africa	Total
No. in study population	39 368	5104	44 472 (100)[a]
Age group			
<20 years	1719	144	1863 (4.2)
20–29 years	11 462	935	12 397 (27.9)
30–39 years	7282	1202	8484 (19.1)
40–49 years	8477	1416	9893 (22.2)
50–59 years	6435	881	7316 (16.4)
>59 years	3932	517	4449 (10.0)
Age unknown	61	9	70 (0.2)
Male: female ratio	1:1.096	1:0.773	1:1.053
Duration of stay			
1–3 weeks	36 883	4176	41 059 (92.3)
4–52 weeks	2303	889	3192 (7.2)
Unknown	182	39	221 (0.5)
No. who replied to second questionnaire[b]	37 564	4638	42 202 (94.9)

[a] Figures in parentheses are percentages.
[b] A total of 35 967 travellers answered after the first mailing, 3073 after the second, and 3162 were interviewed by telephone. Overall, 75.7% of all the passengers on board the aircraft answered the second questionnaire.

Pre-travel medical advice

Almost all the travellers were aware of the risk of malaria infection (Table 2). Family physicians, vaccination centres, and pharmacies were the main medical sources of such information in all the home countries, while specialists in tropical medicine had been consulted by 5.9% of the travellers. Depending on the country, 4.7–19.0% of travellers did not

Table 2: **Sources of pretravel information about malaria and use of protective measures against mosquito bites and of chemoprophylaxis by travellers to Africa**

	Country of residence of traveller: Switzerland (n=25 616)[a]	Federal Republic of Germany (n=11 433)	Austria (n=2937)	France (n=1800)	Italy (n=1789)	Total[b] (n=44 472)
Information about malaria:						
% informed about risk	99.1	99.3	99.1	98.8	98.6	99.0
% advised by medical source[c]	91.4	90.3	92.3	82.4	81.0	90.3
% advised by travel agent or read brochure[c]	50.0	47.1	40.7	33.8	38.3	46.9
% who used one or more measures against mosquito bites	58.1	57.2	43.4	46.2	44.8	55.6
% who used chemoprophylaxis:	98.4	97.3	98.4	96.6	90.9	97.6
Regularly while abroad	95.4	94.0	95.0	90.7	84.8	94.1
Fully compliant (abroad and after return)	59.6	54.6	52.9	31.6	34.1	55.4
Never	1.6	2.7	1.6	3.4	9.1	2.4

[a] Figures in parentheses are the number of travellers surveyed.
[b] The country of residence of 882 of the travellers was somewhere other than the five countries shown; while for 15 travellers it was not known.
[c] Several answers were possible.

consult a medical source before their journey; apparently, they relied on knowledge from previous journeys or on advice from friends or travel agencies. This behaviour was more often observed among business travellers (25.0%) than vacationers (9.0%) ($P < 0.001$). Only 46.9% of the travellers stated that they had been informed about the risks of malaria by travel agents, through reading brochures, or by airline staff.

Personal protection against mosquito bites

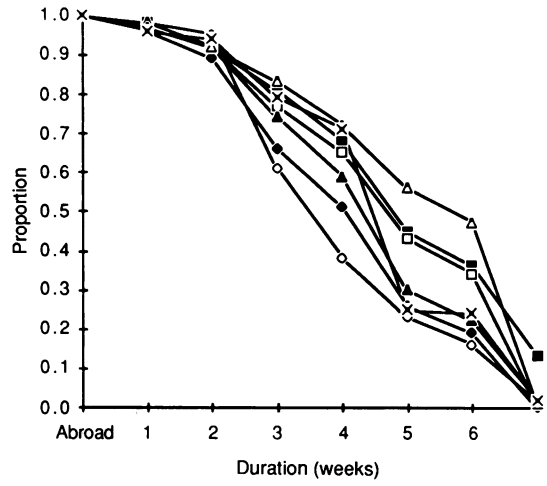
One or more measures to avoid mosquito bites were used by 56% of the travellers (Table 2): 31.7% used insecticides; 23.5% a mosquito net; 21.2% an insect repellent; and 19.5% wore long clothing after dusk. Many travellers stayed in air-conditioned hotels where mosquito nets are not needed. Of all the travellers surveyed, 4.5% tried to avoid mosquito bites by using each of the other three measures. Not using personal protection measures was associated in the logistic regression analysis with a shorter stay, a high number of previous visits to the tropics, being male, or a younger age ($P < 0.0001$ for each variable). On the other hand, those who took no chemoprophylaxis did carry out a greater proportion of measures against mosquito bites. The use of such measures did not significantly reduce the risk of malaria, but the regularity of their use was not investigated.

Use of chemoprophylaxis

Most travellers (94.1%) stated that they used chemoprophylaxis regularly while abroad (Table 2). Depending on their country of residence, 37.5–71.8% (mean, 67.8%) of the travellers continued to take chemoprophylaxis regularly for at least 4 weeks after their return (Fig. 1). Thus 31.6–59.6% (mean, 55.4%) of the travellers were fully compliant before and during travel and for 4 weeks after their return. Compliance was 60.4% for weekly, 43.7% for daily, 53.3% for twice weekly, and 37.1% for thrice weekly ($P < 0.001$) regimens. Other factors that reduced good compliance were a stay abroad that exceeded 3 months (29.2% versus 57.0%, $P < 0.001$) and several previous journeys versus the first journey to the tropics (54.4% versus 58.9%, $P < 0.001$). Depending on the prophylactic medication involved, severe adverse drug reactions were experienced by 1.5–4.4% ($P < 0.001$) of travellers, causing at least 200 of them to stop before 4 weeks of returning home (Table 3).

The drug regimen taken depended on the travellers' home country. In addition to prophylactic medication against malaria, 37.9% of all travellers took any other drugs while abroad, and 7.3% used two or more other drugs.

Fig. 1. **Plots showing the duration of malaria chemoprophylaxis after the study travellers returned from Africa to various European countries.** ● = Austria; ○ = Belgium; ■ = France; □ = Federal Republic of Germany; ▲ = Italy; △ = Switzerland; × = Netherlands.



Adverse drug reactions to malaria chemoprophylaxis

All the drugs used for chemoprophylaxis were frequently associated with adverse reactions. These were rated by the travellers as mild in approximately 60% of instances, as moderate in 30%, and as severe in 10% for each regimen. For travellers who did not take chemoprophylaxis, the background incidence of "reactions" was 4.1%. Table 3 shows the rates of adverse drug reactions that occurred during the entire chemoprophylaxis period. Less than 20% of such reactions were attributed to proguanil, PYR/SDX, or the half-dose combination mefloquine (125 mg)/sulfadoxine (250 mg)/pyrimethamine (12.5 mg). In contrast, rates of greater than 25% were reported after having taken amodiaquine + PYR/SDX, amodiaquine alone, full dose mefloquine/PYR/SDX, or chloroquine + PYR/SDX. The differences in rates of adverse reactions between the various regimens were significant.

"Redness of the skin" was attributed more often to PYR/SDX (3.0%) than to chloroquine (2.1%) ($P < 0.001$) or mefloquine (2.4%) but the differences were not significant. This symptom was reported even more frequently when PYR/SDX was taken together with amodiaquine (5.1%) ($P < 0.002$) or chloroquine (3.8%) (not significant, $P = 0.02$), as compared with the chloroquine + proguanil regimen (1.7%). Itching was reported by 2.1–7.2% of the travellers (not significant). Within the "other"

Table 3: **Distribution of adverse drug reactions and subsequent medical consultations or discontinuation of antimalarial drugs by travellers over the entire prophylaxis period[a]**

Drug	No.	% of adverse drug reactions: Cutaneous	Nausea	Other	Total	% who consulted a doctor	% who discontinued medication	P(obs)/ P(exp)[c]
Chloroquine:								
300–450 mg base/week	3796	6.1	11.1	8.9	21.2	2.1	1.7	1.03
600–700 mg base/week	5375	6.4	12.0	9.8	22.7	2.4	2.4	1.10
Amodiaquine	1114	4.6	20.3	12.3	29.4	3.9	4.2	1.40
Mefloquine	2780	5.7	11.5	8.8	21.2	2.2	1.5	0.99
Proguanil	107	4.7	2.8	3.7	11.2	1.9	0	0.54
PYR/SDX[d]	17 036	6.2	9.4	6.4	17.9	2.0	2.1	0.89
Chloroquine + PYR/SDX	4741	7.4	14.6	10.7	25.6	2.8	2.2	1.20
Amodiaquine + PYR/SDX	778	10.0	32.0	16.1	44.1	6.7	4.4	2.07
Mefloquine/PYR/SDX:[e]								
Full dose	128	10.9	15.6	9.4	27.3	3.1	4.4	1.42
Half dose	332	3.9	9.3	7.2	16.0	2.1	2.9	0.83
Chloroquine + proguanil	231	5.2	13.0	11.7	23.8	3.0	3.2	1.12

[a] The information shown applies to the pooled data from both questionnaires.
[b] A total of 5034 travellers were excluded because either the dosage of antimalarial drugs taken was not known or they took no chemoprophylaxis.
[c] P(exp) was calculated using a multiple logistic regression analysis with adverse drug reactions as the dependent variables. The independent variables were: sex, age, language, and other drugs taken. P(obs) was expressed as the number of persons who took antimalarial drugs and had adverse reactions divided by the total number of observations for travellers in this group.
[d] PYR = pyrimethamine; SDX = sulfadoxine.
[e] Full dose = 250 mg mefloquine/25 mg PYR/500 mg SDX, half dose = 125 mg mefloquine/12.5 mg PYR/250 mg SDX.

category of adverse drug reactions summarized in Table 3, significant differences were noted for diarrhoea (0.8–6.5%; highest for amodiaquine + PYR/SDX), visual disorders (0–2.4%; highest for chloroquine + proguanil), and tiredness (0–3.7%; highest for amodiaquine + PYR/SDX). Psychological or psychiatric disorders were noted for 0–0.6% of the travellers (not significant): two patients who had taken chloroquine, one who had taken chloroquine + PYR/SDX, and one who had taken mefloquine, needed medical treatment, the latter for a depression that lasted for a period of 9 months. Nineteen users of mefloquine had concomitantly taken betablockers or other cardioactive drugs, but none reported cardiovascular side-effects. Subjectively severe skin reactions were noted by approximately 1% of the users of any drug regimen. Overall, a doctor was consulted for adverse drug reactions by 2.4% of the travellers during (1.0%) or after (1.5%) their stay abroad. Multiple logistic regression analysis showed particularly high rates of adverse reactions when additional medication was taken, among women and among younger age groups ($P < 0.0001$ for each variable).

The adverse drug reactions that were followed by hospitalization are listed in Table 4. Four fatal cases were recorded: two from agranulocytosis due to amodiaquine; one of Lyell's syndrome due to an excessive dosage of sulfonamides (the patient took chloroquine + PYR/SDX and three double-strength tablets of sulfamethoxazole/trimethoprim against a suspected urinary tract infection); the occurrence of vasculitis in the fourth case may be attributable either to chronic active hepatitis with cirrhosis of the liver or to the patient having taken PYR/SDX. In addition to the three patients who were hospitalized with drug-induced toxic hepatitis, there were 17 further patients who were treated at home for hepatitis, but the attending physician was unable to differentiate between toxic and non-A, non-B hepatitis. The patient with thrombocytopenia that was attributed to chloroquine had a recurrence; he had also previously experienced spontaneous bleeding while taking chloroquine.

Adverse drug reactions following self-treatment

A total of 7867 travellers had obtained three tablets of PYR/SDX for the self-administered therapy of presumed malaria. The tablets were used by 427 of the travellers (5.4%); of these, 7.0% reported mild side-effects, usually nausea.

A total of 335 out of 9395 travellers (3.6%) took three 250-mg tablets of mefloquine for presumptive treatment after PYR/SDX chemoprophylaxis. Vertigo, nausea, and other side-effects were reported by 27.8% of these individuals, who often required bed-rest for one or more days.

Table 4: **Hospitalized patients with probable or possible adverse drug reactions, rates of hospitalization and fatal outcome, depending on the chemoprophylaxis, for the travellers surveyed**

Antimalarial drug(s)	Main symptom(s)	Outcome	Rate (per 1000 journeys): Hospitalization	Fatal adverse drug reaction
Amodiaquine	Agranulocytosis[a]	died		
Amodiaquine[b]	Agranulocytosis[a]	died		
Amodiaquine	Agranulocytosis[a]	cured	4.5[a]	1.8[a]
Amodiaquine[c]	Agranulocytosis[a]	cured		
Amodiaquine	Hepatitis (toxic)[a]	cured		
Chloroquine	Gastrointestinal[a,d]	cured		
Chloroquine	Gastrointestinal[a,d]	cured		
Chloroquine	Erythema [a,d]	cured	0.5[a]	0
Chloroquine	Thrombocytopenia (recurrent)[a]	cured	0.6[a]	
Chloroquine	Psychosis[a]	cured		
Chloroquine	Psychosis [f]	cured		
PYR/SDX[g]	Vasculitis (acute) [f]	died		
PYR/SDX	Hepatitis (toxic)[a]	cured	0.1[a]	0[a]
PYR/SDX	Hepatitis (toxic)[a]	cured	0.2[a]	0.1[a]
PYR/SDX/chloroquine + sulfamethoxazole/ trimethoprim	Agranulocytosis and Lyell's syndrome [f]	died		
Proguanil + chloroquine	Bleeding duodenal ulcer[f]	cured	4.3[a]	0

[a] Definite or probable association with antimalarial drug(s).
[b] Initially took chloroquine as prophylaxis.
[c] Took also one dose of pyrimethamine/sulfadoxine.
[d] Treated in Africa (all other cases were diagnosed and treated in Europe).
[e] Includes also travellers who had only a possible adverse drug reaction.
[f] Possible association with antimalarial drug(s).
[g] PYR = pyrimethamine; SDX = sulfadoxine.

Malaria

Of the 156 malaria infections that were allegdly diagnosed by blood smear, 35 were excluded because of other diagnosis or insufficient data. The majority of the remaining 121 cases of malaria were due to *P. falciparum* (Table 5). The shortest incubation time was 7 days. Among the 80 patients who had stayed abroad for up to 4 weeks, 30 (37.5%) were diagnosed there; and of the 59 malaria infections that were diagnosed in Europe, 44 (74.6%) had onset of symptoms within 2 weeks of returning from holiday.

Based on the data for the 16 travellers with malaria who had taken no chemoprophylaxis, the average incidence per month was estimated to be 15.2 per 1000 in East Africa and 24.2 per 1000 in West Africa. When all malaria infections are considered, the incidence of malaria in East Africa varied according to the season, the highest incidences being observed in the rainy spring and summer, whereas few cases where diagnosed in the dry season.

For compliant travellers, the incidence of malaria per month of exposure and the efficacy of the main drug regimens are shown in Table 6. Mefloquine, chloroquine + PYR/SDX, PYR/SDX alone, or chloroquine (600–700 mg base per week) exhibited a significant advantage compared with no chemoprophylaxis at all. In contrast, use of a lower dose of chloroquine (300–450 mg base per week) did not produce a significant protective effect and was inferior to the higher dose ($P = 0.005$). Data for proguanil (two malaria cases with good compliance, 22 person-months' exposure) and pyrimethamine/sulfalene (no malaria cases) are not included in Table 6 because the number of users of these regimens was too low. According to the results of a logistic regression analysis, the only host factors that influenced the efficacy of the regimen were drug use and duration of stay in Africa.

Four fatal cases of falciparum malaria were reported. All four patients had regularly taken two or three tablets of chloroquine phosphate (150 mg base; Resochin®) per week, beginning 1–2 weeks before, continuing throughout their 2–3 weeks' stay in Kenya, and extending until the onset of symptoms 1–9 days after their return. All four were hospitalized in the Federal Republic of Germany within 4–5 days of the symptoms appearing; three died in hospital within 1 day of admission. The case-fatality rate was 3.3% for all malaria cases. No other fatalities caused by malaria or adverse drug reactions were reported by the embassies of European countries in Africa or by air rescue organizations.

Table 5: **Characteristics of the malaria cases that were diagnosed by blood smear**

	East Africa	West Africa	
	No.	No.	Total
No. of cases evaluated	81 (66.9)[a]	40 (33.1)	121 (100)
Place of diagnosis:			
Africa	32 (39.5)	30 (75.0)	62 (51.2)
Europe	49 (60.5)	10 (25.0)	59 (48.8)
No. of previous journeys to the tropics:			
None	38 (46.9)	14 (35.0)	52 (43.0)
One or more	43 (53.1)	26 (65.0)	69 (57.0)
Parasitology:			
P. falciparum	55 (93.2)	16 (84.2)	71 (91.0)
P. vivax	4 (6.8)	2 (10.5)	6 (7.7)
P. malariae	0 (0)	1 (5.3)	1 (1.3)
Not specified	13 —	6 —	19 —
No response from the physician[b]	9 —	15 —	24 —
Compliance with malaria chemoprophylaxis:			
Good	55	25	80
Bad	16	9	25
No chemoprophylaxis	10	6	16

[a] Figures in parentheses are percentages.
[b] Not substantiated, but there was a convincing history with details of smear results.

Discussion

For a randomized study comparing the efficacy and adverse reactions of the various regimens of malaria chemoprophylaxis recommended to Europeans who intend to visit Africa, one would ideally have to recruit a large sample of travellers who were equally at risk of malaria. All adverse drug reactions and cases of malaria would have to be competently investigated. The follow-up study that we have reported here, although it does not meet these criteria, nevertheless provides important data for developing prophylaxis recommendations—which are often based on impressions and opinions rather than on a systematic quantitative approach (*18*). Since we investigated more travellers than were included in a study of scheduled airline passengers (*19*) that used virtually the same questionnaire, the data we obtained can be used to calculate drug efficacy rates.

The potential biases in the study include those inherent to self-administered questionnaires, e.g., self-reported adverse drug reactions, an over-representation of short-term vacationers (92% in the study population, as compared with 77% for all visitors to Kenya; Kenya Ministry of Tourism, personal communication, 1988), and the lack of verification of all malaria cases. Nevertheless, 80.2% of the self-reported cases of malaria were confirmed also by a physician's report—the main reason for the missing

Table 6: **Incidence of malaria per month per 1000 travellers among the study population and efficacy of various regimens of chemoprophylaxis[a]**

	No. of cases of malaria		No. of person-months' exposure		Incidence		Significance compared with no prophylaxis in East Africa[b]			Prophylactic efficacy (%)	
Chemoprophylaxis	East Africa	West Africa	East Africa	West Africa	East Africa	West Africa	P (χ^2 test)	*RR*	95% confidence interval	East Africa	West Africa
None	10	6	656	248	15.2	24.2	—	1.0	—	0	0
Chloroquine:											
300–450 mg base/week	17[c]	16	953	570	17.8	28.1	NS[d]	0.8	0.4–1.8	−17.1	−16.1
600–700 mg base/week	7	4	1280	359	5.5	11.1	0.03	2.8	1.1–7.3	64.1	53.9
Amodiaquine	4	1	382	62	10.5	16.1	NS	1.5	0.5–4.6	31.3	33.5
PYR/SDX[e]	18	1	6226	109	2.9	9.2	0.003	5.3	2.4–4.3	81.0	62.0
Mefloquine	1[f]	0	1102	8	0.9	—	0.003	16.8	2.2–130.8	94.0	—
Chloroquine + PYR/SDX	2	0	1688	33	1.2	—	0.003	12.9	2.8–58.4	92.2	—
Amodiaquine + PYR/SDX	1	0	307	1	3.3	—	NS	4.7	0.6–36.4	78.6	—
Mefloquine/PYR/SDX[g]	0	—	134	—	0	—	NS	—	—	100.0	—
Various	5	3	983	336	—	—	—	—	—	—	—
Total	65	31	13 711	1726	—	—	—	—	—	—	—

[a] Data refer to travellers who had good compliance with the chemoprophylaxis. All populations with 60 person-months' exposure were excluded.
[b] Comparison of two rates. Because of the smaller sample size, there were no significant differences in West Africa.
[c] Including four fatal cases.
[d] NS = not significant.
[e] PYR = pyrimethamine; SDX = sulfadoxine.
[f] Remained anonymous; follow-up impossible.
[g] Half dose (125 mg mefloquine/12.5 mg PYR/250 mg SDX).

reports being the failure to create patient files in West Africa. The potential source of exaggeration by false-positive reports is probably more than balanced by the 129 cases of malaria that were diagnosed only clinically, and which were not included in the analysis.

Almost all the travellers had been informed about the existence of a malaria risk. However, only a small minority of them took three important measures against mosquito bites. It is not known whether the 95% who did not do so were unaware of such measures or whether they chose not to follow them. Travellers should be urged systematically to follow measures against mosquito bites, but surveys are needed to determine how this can best be implemented.

Non-compliance with malaria chemoprophylaxis occurred mainly among long-term travellers while they were still in Africa. Additionally, only two-thirds of the travellers continued taking chemoprophylaxis until 4 weeks after their return, as recommended by WHO (*20*).

A large proportion of travellers reported adverse drug reactions, which were usually mild. The incidence of side-effects depended primarily on the type of drug(s) used; for chloroquine, dosage played only a negligible role, but seemed more relevant with mefloquine/PYR/SDX. PYR/SDX was associated more often with "redness of the skin", which may possibly have a similar pathophysiological origin as severe cutaneous adverse drug reactions. When taken for prophylaxis, mefloquine was tolerated to the same extent as the more traditionally used antimalarial drugs, and no alarming reactions were reported. In contrast, 750 mg of mefloquine, which was recommended for the self-therapy of presumed malaria in patients who had taken PYR/SDX prophylaxis, was associated with adverse reactions (usually very disagreeable vertigo and nausea) in 28% of patients. In a trial that evaluated a final prophylactic dose given immediately after leaving the malarious zone, 59% of healthy Swiss travellers experienced adverse reactions after having taken 750 mg of mefloquine.[c]

Severe adverse drug reactions were reported by 16 patients. The results confirm the high risk of amodiaquine-induced agranulocytosis and toxic hepatitis. The incidence of adverse reactions of 6.5 per 1000 users of this drug (fatalities: 2.6 per 1000) is slightly higher than that found in most other, purely retrospective (*12*, *13*, *21*)[d] surveys that may have been biased by underreporting. The results of the study cannot be used to draw conclusions about the risks associated with taking PYR/SDX, since the two fatalities among travellers who took this regimen had no more than a possible association with the chemoprophylaxis. Previous surveys have linked this drug combination with attack rates for severe cutaneous adverse reactions of 1 per 5000–8000(*10*) in the USA, and of 1 per 2600–10 800 (prescription data) or 1 per 9600–39 900 (pharmaceutical data) in the United Kingdom (*22*). In Switzerland, from 1985 to 1988, the incidence of severe cutaneous adverse drug reactions with PYR/SDX was 1 per 80 000 travellers (D. Chen, unpublished observation, 1988) which is greater than that previously reported for this country (*23*). Both amodiaquine and PYR/SDX were still being used in 1989 by travellers to Africa (R. Steffen, unpublished data), although amodiaquine has been withdrawn for continuous malaria chemoprophylaxis by the manufacturer and PYR/SDX is no longer recommended for chemoprophylaxis by WHO (*20*) or, to the best of our knowledge, as a first-choice prophylactic agent by any national experts group.

Chloroquine was only rarely associated with adverse reactions that needed hospitalization: these included gastrointestinal symptoms (*8*), erythema and more severe cutaneous reactions (*8*, *24*, *25*), thrombocytopenia (*26*) and psychosis (*27*, *28*). Psychosis has also been described after mefloquine use, particularly in therapeutic dosages (*29*, *30*), and it has therefore recently been suggested that for self-therapy a dose of 1000 mg mefloquine should not be exceeded (*31*). In our sample of 3386 travellers who took mefloquine alone or with PYR/SDX, one patient required outpatient treatment for depression. This was no more than possibly associated with the medication, since the symptoms persisted for 7 months after the individual stopped taking the drugs. No acute brain syndromes were observed.

Malaria occurred more frequently among the travellers in the study than had previously been estimated (*32*). This is principally because of underreporting to national surveillance bodies in industrialized countries and because cases treated overseas are missed by surveillance. Of the 27 cases that were reported among Swiss residents after returning home in the 1985–88 follow-up period, only 12 (44.4%) had been notified to the Federal Office of Public Health. Additionally, surveillance is unable to record cases that occur abroad. The estimated average monthly risk of malaria in unprotected travellers (1 in 41 in West Africa and 1 in 66 in East Africa) is comparable with the incidence among U.S. Peace Corps Volunteers (*33*).

Mefloquine was highly effective in preventing malaria. Chloroquine given at a dosage of 600–700 mg base per week appeared to provide better protection than the 300 mg base per week regimen, which was not

[c] **Pfister, M.** [*Undesired effects of mefloquine after final malaria prophylaxis taken on journeys to the tropics*]. Thesis. University of Bern, 1988 (in German).

[d] See footnote *a*, p. 314.

efficacious. Some pharmacokinetic studies have also suggested that this lower dosage may be less effective (*34*). Additionally, the acid vesicles of resistant *P. falciparum* release chloroquine over 40 times faster than those of the susceptible parasites (*35*), and it is plausible that this release mechanism may be partly compensated by the higher chloroquine dosage. The protective effect of chloroquine that we found is lower than that reported in a previous retrospective analysis (*36*), because in the latter study the duration of stay, compliance with the regimen, or the number of cases treated abroad could not be taken into account. The efficacy of prophylactic regimens calculated in this study is based on numerator data (malaria infections during and after travel) and denominator data (number of travellers using, and not using, prophylaxis) in a precisely defined population. This method is likely to provide more accurate results than studies that obtain numerator data from surveillance systems and denominator data from estimates of the numbers of travellers using chemoprophylaxis (*36, 37*).

In conclusion, while mefloquine and the higher chloroquine dosage appeared to offer the best malaria prophylaxis in East Africa, and the higher chloroquine dosage also in West Africa, additional data are needed to assess the chloroquine + proguanil regimen. The extent of increasing drug resistance should also be monitored. The efficacy of the two chloroquine regimens (300 mg versus 700 mg base per week) needs to be investigated in controlled chemoprophylaxis studies of non-immune subjects in tropical Africa. Even if chemoprophylaxis with chloroquine in areas with chloroquine-resistant *P. falciparum* may possibly sometimes prevent death (*38*), such a suboptimal regimen also, if taken regularly, will not prevent death with certainty.

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Résumé

Chimioprophylaxie du paludisme chez des touristes européens en Afrique tropicale: application, réactions indésirables et efficacité

Pour savoir quelles sont les connaissances, les attitudes et les pratiques concernant les mesures de prévention du paludisme, de même que les effets indésirables et l'efficacité de ces dernières, un autoquestionnaire a été distribué à des voyageurs européens sur des vols de retour d'Afrique tropicale vers l'Europe. Entre 1985 et 1988, le questionnaire a été rempli par 44 472 passagers (80,1% de ceux qui étaient à bord) sur 242 vols revenant vers leur pays. Un questionnaire de suivi a été également rempli par 42 202 (94,9%) de ces voyageurs trois mois plus tard. Presque tous savaient quels étaient les risques de paludisme, mais 10% se fiaient seulement à des conseils provenant de sources non médicales. Si 55,6% d'entre eux appliquaient au moins une mesure contre les piqûres de moustiques, seuls 4,5% avaient adopté trois de ces mesures (utilisation de répulsifs et d'insecticides et port de vêtements longs dès la nuit tombée). L'observance de la chimioprophylaxie était rapportée par 57,0% des voyageurs qui passaient moins de trois mois en Afrique, contre 29,2% de ceux qui restaient de 3 à 12 mois. Suivant le traitement antipaludique suivi, de 11 à 44% des voyageurs avaient ressenti des effets indésirables, et quatre décès ont été attribués à la chimioprophylaxie. L'incidence du paludisme par mois d'exposition était, pour les voyageurs qui n'avaient pas suivi de chimioprophylaxie, de 15,2 pour 1000 en Afrique orientale, et de 24,2 pour 1000 en Afrique de l'Ouest. En Afrique orientale, l'efficacité prophylactique des traitements antipaludiques actuellement recommandés (par rapport à ce qui se passe en l'absence de chimioprophylaxie) était de 0 pour une dose de 300 mg de chloroquine base par semaine (4 décès dus au paludisme), de 64,1% pour une dose de 600 mg de chloroquine base par semaine ($P=0,03$), et de 94,0% pour la méfloquine ($P\leqslant 0,003$).

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